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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/651,584	08/30/2003	Vit Lauermann		8871

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EXAMINER	
CHANDRA, GYAN	
ART UNIT	PAPER NUMBER
1646	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/651,584	LAUERMANN, VIT	
	Examiner	Art Unit	
	GYAN CHANDRA	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *10 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *18-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 10/10/2008 is acknowledged and fully considered.

Status of Application, Amendments, And/Or Claims

Claims 1-23 are pending.

Claims 18-23 remain withdrawn from further consideration as being drawn to a nonelected Invention.

Claims 1-17 are under examination.

Specification

The listing of references in the specification (page 54) is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Response to Arguments

Election/Restrictions

Applicant argues that the restriction election for examination purpose of the invention was made with traverse and therefore, the office should not have made election requirement final. Applicants argue that on page 9 of the office action of 7/9/2008 the non-elected species are recited and therefore the election requirement should be removed altogether.

Applicants' arguments have been fully considered but they are not persuasive in response to restriction election filed on 4/14/2008, applicant did not distinctly and specifically point out the supposed errors in the restriction requirement and therefore, the election was made final. It is noted to applicant that the page 9 of the office action of 7/9/2008 only recited the claims which includes non-elected species but the non-elected species were not examined. Applicant has the option to petition the finality of the action to the office.

Objections/Rejections- *maintained*

Specification

The objection to abstract because the abstract comprises more than 150 words is withdrawn in view of Applicant's amendment of the abstract filed on 10/10/2008. However, the disclosure remains objected because it discloses either a nucleic acid sequence, amino acid sequence or both (e.g., pg. 30, 44) and these sequences are not in compliance as per 37 CFR 1.821-1.825. It is noted that a sequence identifier ("SEQ ID NO:X") must be used in order to be in sequence compliance as per 37 CFR 1.821-1.825.

Applicant argues (page 1 of Response) that if the Examiner can not find sequences recited in the specification in the sequence listing then such a sequence can be provided upon request.

Applicant's arguments have been fully considered but they are not persuasive because page 3 of the Office Action of 7/9/2008 clearly indicates that the specification (e.g., pg. 30 and 44) recites sequences which should be followed by a sequence

identifier ("SEQ ID NO: X"). For example sequence in page 30, line14, discloses an amino acid sequence: GGNGG, and line 15, discloses a sequence KDEL. Additionally, page 44, line 6 of the specification discloses a peptide sequence "HSSKLQ".

Claim Objections

Claims 2-5, 8 and 10-11 remain objected to because of the following informalities:

Claims 2-3 are objected for reciting a number of non-elected first moieties (i.e., a soluble receptor, a cyclic peptide, a single chain antibody, a receptor, a chemokine, a nucleic acid, a peptide-lipid conjugate, a hormone or an antigen).

Claim 4 is objected for reciting a number of non-elected inhibitors (a peptide-nucleic acid inhibitor, a pepducin inhibitor, a nucleic acid/protein conjugate inhibitor, a receptor inhibitor, and others).

Claim 5 is objected for reciting a number of active agents (a chemical drug, a nucleic acid, a monoclonal antibody, a bispecific antibody, a single chain antibody, a cyclic peptide, a peptducin, a kinin system, a coagulation system and others).

Claims 8 and 10 are objected for reciting a number of second moieties (a lipid, a glycolipid, a nucleic acid, a phospholipid, a carbohydrate or many peptides having amino acid sequences e.g., SEQ IDs 2, 3, 4, 5,..... 108 and 109).

Claim 11 is objected for reciting a number of reagents (i.e., a lipase, nuclease, or a glycolytic enzyme).

Applicant argues that restriction should be withdrawn. Applicant's arguments have been addressed above. It is noted to applicant that the non-elected (non-allowed) species should be cancelled upon the allowance of any allowable subject matter.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 6, the phrase "second moiety is embedded within the first moiety" renders the claim indefinite.

Applicant argues that "the second moiety is the second moiety" and that the first moiety and the second moiety are a part of one molecule. Claim 6 recites "said second moiety is embedded within the first moiety". Applicant argues that they are operatively linked but the claim recites "said second moiety is embedded within the first moiety". It is not clear how the second moiety can be structurally embedded in the first moiety. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 112, first paragraph-enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an inhibitor comprising (a) first moiety operably linked to (b) a second moiety, does not reasonably provide enablement for an inhibitor comprising (a) first moiety operably linked to (b) a second moiety wherein specific cleavage of second moiety causes reduction of binding, or activity of said inhibitor for the reasons of record in pg. 5-8 of the office action of 7/9/2008 and as discussed below.

Applicant argues that the references Thorpe et al, D'Amico, Gillies et al and Mhaka et al do not teach an inhibitor which is deactivated by a reagent produced by a target cell. Applicant argues that all the examples taught in the specification are inhibitors and that by a routine experimentation one skilled in the art would know that such inhibitors are deactivatable by a reagent produced by a target cell.

Applicant's arguments have been fully considered but they are not persuasive for the reasons of record in pg. 5-8 of the office action of 7/9/2008 and because although making a fusion protein from two or more proteins are known in the art, neither the art nor the specification teaches that the cleavage of a fusion protein by removing second moiety would always result in reduced activity of said fusion protein. This can only happen when a fusion protein is always more inhibitory than any moiety (the first moiety or the second moiety) when used alone. Therefore, it is unpredictable and would require a large amount of experimentation to determine if the inhibitors comprising (a) first

moiety operably linked to (b) a second moiety when specifically cleaved the second moiety would more likely than not result in reduction of binding, or activity of said inhibitor. Therefore, it is unpredictable how one of the skill in the art can practice the instantly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

For the purpose of comparing the claims with the prior art, it is noted that "an inhibitor which is deactivatable by a reagent produced by a target cell comprising: (a) first moiety operably linked to (b) a second moiety wherein specific cleavage of second moiety causes reduction of binding, or activity of said inhibitor." is being interpreted as "an inhibitor that can be deactivated by any reagent produced by a target cell, wherein said inhibitor would be less active upon cleavage of the moiety only when moieties (a) and (b) are more active together than any of the two moieties alone." It is noted that (a) first moiety and (b) second moiety are not produced in nature as a hybrid molecule.

Claims 1-5, 7-9, 11, 13-17 remain rejected under 35 U.S.C. 102(b) as being anticipated by Thorpe et al (US Patent No. 6,093,399).

The instant claims are broadly drawn to an inhibitor which is deactivatable by a reagent produced by a target cell comprising: (a) first moiety operably linked to (b) a second moiety wherein specific cleavage of said second moiety causes reduction of binding, or activity of said inhibitor, wherein said first moiety is a polypeptide, a peptide, an antibody, a bispecific antibody (claims 2-3); wherein said inhibitor is a bispecific

antibody inhibitor (claims 4); wherein said active agent is a bispecific antibody or a coagulation factor (claim 5); wherein said first and second moieties are connected by a peptide, or a chemical linker (claim 7); wherein second moiety is selected from the group consisting of a peptide, a lipid, a polypeptide, a carbohydrate, a polysaccharide, a glycolipid, a nucleic acid or a conjugate thereof (claim 8); wherein said second moiety is a peptide which comprises a sequence cleavable by protease (claim 9); wherein said inhibitor of claim 1 is selected from the group consisting of a protease, a lipase, a nuclease, or glycolytic enzyme (claim 11); wherein said reagent is produced by endothelial cells, activated or proliferating endothelial cells or tumor cells (claim 13); wherein the inhibitor alone or inhibitor with an active agent is in a biodegradable polymer, in a slow release implant, in a microcapsulated composition, or conjugate with a biodegradable polymer (claim 14); wherein the inhibitor of claim 1 further comprises or associates with a recognition domain that binds to a target cell surface marker, an extracellular matrix or component thereof (claim 15); wherein said recognition domain binds to tumor cells (claim 16); and wherein said recognition domain is selected from the group consisting of an antibody, a monoclonal antibody, a bispecific antibody..... a tissue factor or compositions and variants thereof (claim 17).

Applicant argues (page 3 of Response) that the interpretation of the instant claim as "any inhibitor that can be deactivated by any reagent produced by a target cell" changes meaning of the claims as filed. Applicants argue that the reference Thorpe et al teach a non-specific cleavage by a protease.

Applicant's arguments have been fully considered but they are not persuasive for the reasons of record in pg. 8-11 of the office action of 7/9/2008 and because the instantly claimed invention is drawn to "an inhibitor which is deactivatable by a reagent of target cell" is not directed to a specific inhibitor which is cleavable by a specific reagent (i.e., a specific protease) and therefore, during patent examination, the claims are given the broadest reasonable interpretation consistent with the specification. See In re Morris, 127 F.3d 1048, 44 USPQ2d 1023 (Fed. Cir. 1997). Additionally, applicant's arguments that the reference Thorpe et al teach a non-specific cleavage by a protease have been fully considered but they are not persuasive because the specification does not define the term "specific cleavage" and therefore, the teachings of Thorpe et al that a fusion protein is cleaved by endogenous proteases present in target tissues (tumor cells) for example, metalloproteinases, thrombin, factor Xa, plasmin (col.88, lines 28+) would meet the instantly claimed limitation. The proteases taught by Thorpe et al have a specific cleavage recognition site, for example Chattopadhyay et al (J. Biol. Chem. 267: 12323-12329, 1992) teach that protease Xa recognizes site "Arg-Ile (page 12323, right column). It is noted that the reference Chattopadhyay is applied to support the state of the art and not as a prior art. Additionally, Polayes et al (Focus, 16: 2-5,1994) teach that factor Xa is a site specific protease (page 2, 1st paragraph). It is noted that the reference Polayes et al is applied to support the state of the art and not as a prior art. Therefore, the prior art of the record anticipates the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 10 and 12 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Thorpe et al as applied to claims 1-5, 7-9, 11, 13-17 above, and further in view of Mhaka et al (Bioorg. Med. Chem. Letters 12: 2459-2461, 2002); or Thorpe et al as applied to claims 1-5, 7-9, 11, 13-17 above, and further in view of D'Amco et al (US Patent No. 6,368,598 published on 4/9/2002).

The instant claims are further drawn to an inhibitor which is deactivatable by a reagent produced by a target cell comprising: (a) first moiety operably linked to (b) a second moiety wherein specific cleavage of said second moiety causes reduction of binding, or activity of said inhibitor, wherein second moiety is SEQ ID NO: 17 (HSSKLQ) (claim 10); and wherein said reagent is a prostate specific antigen (claim 12).

Applicant argues (page 3 of Response) that the references Thorpe et al and Mhaka et al do not teach an inhibitor which is deactivatable by a reagent produced by a target cell. Applicant argues that even if the combined teachings of Thorpe et al, Mhaka et al and D'Amico et al would work, the idea as claimed in the instant invention has not been patented.

Applicant's arguments have been fully considered but they are not persuasive for the reasons of record in pg. 11-13 of the office action of 7/9/2008 and because from the combined teachings of Thorpe in view of Mhaka et al; or Thorpe in view of D'Amico et al, it would have been obvious to one of the skill in the art to use a peptide such as HSSKLQ for targeted delivery in tumors such as prostate metastasis where a reagent such as PSA cleaves the peptide HSSKLQ.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GYAN CHANDRA whose telephone number is (571)272-2922. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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